A I D S TREATMENT N E W S

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AIDS Treatment News

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Statement of Purpose:

AIDS Treatment News reports on experimental and standard treatments, especially those available now. We interview physicians, scientists, other health professionals, and persons with AIDS or HIV; we also collect information from meetings and conferences, medical journals, and computer databases. Long-term survivors have usually tried many different treatments, and found combinations that work for them. *AIDS Treatment News* does not recommend particular therapies, but seeks to increase the options available.

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Flu Shot Reminder

Influenza shots are definitely recommended for persons with HIV or immune deficiencies. [1] They are often given in October or November, before the flu season begins.

Where can you get the shots? A good place to ask is where you usually get health care.

If that doesn't work, a number of drugstore chains and other organizations have a traveling flu clinic that goes from store to store. These may be available only once at a particular location, and will usually charge a fee, often about $25. The two we checked, CVS and Walgreens, have online locators to find a site near you; many only give shots once, as early as October, so it's a good idea to make plans early.

Note that people with HIV should get the flu shots (**not** the FluMist nasal spray, since that contains a weakened live virus and could be dangerous for persons with immune deficiency; it is only approved for healthy people between the ages of 2 and 49). The shot does not have live virus, and

cannot cause the flu.

In some cases, anti-flu drugs are recommended for people with HIV who are likely to be exposed to someone with the flu. [1]

In the U.S., the proportion of people with HIV getting the annual flu shot has risen "from 28.5% in the 1990 to 41.6% in the 2002 influenza season" [2] -- improvement but still short of the U.S. government goal of 60% by 2010. In comparison, in countries with near-universal healthcare, up to 92% of people with HIV get the shot [2].

Incidentally, the 1990-2002 figures were published in July 2007; it takes a while for the wheels to turn in U.S. medicine and research. A way to deal with this problem is to use real-time data centers when possible.

References

1. The U.S. Centers for Disease Control and Prevention has a flu information page,
http://www.cdc.gov/flu/
It links to a page of information for persons with HIV,
http://www.cdc.gov/flu/protect/hiv-flu.htm
(last updated September 19, 2007 or later, despite references to the 2004-05 influenza season).

2. Gallagher KM, Juhasz M, Harris NS, and Teshale EH. Predictors of influenza vaccination in HIV-infected patients in the United States, 1990-2002. *The Journal of Infectious Diseases.* 2007; volume 196, pages 339-346, or free full text at
http://www.journals.uchicago.edu/JID/journal/issues/v196n3/37548/37548.html

New Kind of Antiretroviral, KP-1461; Clinical Trial Recruiting. Interview with Stephen Becker, M.D.

by John S. James

Summary: KP-1461, an experimental HIV drug already in a phase II trial, works so differently from other antiretrovirals that at first glance it looked like science fiction, and we found it hard to take seriously as a current possibility today. In fact this drug is highly credible, and based on elegant science that goes back at least 25 years. KP-1461 is the only antiretroviral in human use or testing that can eradicate HIV from laboratory cell cultures. No one knows how it will work in people -- but we might know by the second quarter of 2008, when the current phase II trial could be complete. *AIDS Treatment News* interviewed Dr. Stephen Becker, a leading AIDS physician and researcher who is vice president of clinical development at Koronis Pharmaceuticals, in Seattle, Washington.

Background: The scientific story began when Mansfeld Eigen (who had already won a Nobel Prize in chemistry for other work) applied his chemistry and mathematics background to problems in biology, and with Peter Schuster and others developed the concept of quasispecies. Standard Darwinian evolution predicts that the fittest strain of an organism, the one that reproduces fastest in a given environment, will displace the other strains there. But a virus like HIV is different; it is always mutating, and can mutate back and forth between different strains. The result is that HIV, in a patient with advanced infection or AIDS, exists as millions of related strains within the same patient (usually only one was transmitted, and then it evolved within that individual into countless slightly different variants).

This makes HIV hard to treat, because some members of the quasispecies probably already have resistance mutations to a new drug even by chance alone, and these resistant viruses are ready to be selected and become much more prevalent when the drug is started. The conventional approach to this problem is to use combinations of different drugs, hoping to suppress HIV to such a low level that little mutation and evolution can take place. This may suppress the virus for years, but has never succeeded in eradicating it, so patients usually have to stay on treatment for life.

Quasispecies follow different rules than Darwinian evolution. For example, it is possible at least in theory for the strain that reproduces fastest to be replaced entirely by strains that individually reproduce more slowly, but are more fit as a quasispecies. Eigen and Schuster also wrote a well-known book, *The Hypercycle: A Principle of Natural Self-Organization*, published in 1979 on quasispecies and related concepts.

A way to attack a quasispecies as a whole is to increase the already-high mutation rate, leading to an "error catastrophe" and collapse of the population. This approach was used to design the drug now in a phase II trial, KP-1461. KP-1461 is a nucleoside analog, like AZT, 3TC, and the others; once inside the cell it is chemically modified (triphosphorylated) into its active form (called KP-1212), which can replace one of the four bases used to make DNA. (The four bases are adenosine, cytodine, thymidine, and guanosine -- some say that the initials 'ACTG' for the government AIDS clinical-trials network were not just coincidence.) In DNA the bases are paired, forming the famous double helix; cytidine always pairs with guanosine, and thymidine always pairs with adenosine.

KP-1212 can replace cytidine when the viral enzyme reverse transcriptase is building a new copy of HIV, and pair normally with guanosine. It does not terminate the DNA chain. But KP-1212 was chemically designed to be a flexible molecule, such that it can also look like thymidine and then pair with adenosine. This introduces an error that then is locked into the viral DNA.

These errors happen at random, anywhere in the virus; and when they do not kill the virus outright, they accumulate over generations in the DNA of the viral population. The result is eventually an error catastrophe that can wipe out the entire quasispecies, at least in laboratory tests. If you then take the drug away, the virus does not come back. And the cells on which the virus grew are still alive -- cured of the infection.

AZT and the other approved nucleoside analogs terminate the growth of the DNA chain, killing the copy of virus being built. But that copy is easily replaced by other copies that do not have an abnormal error accumulation, so the population as a whole is not damaged. In contrast, KP-1212 continues to add new errors to the population, in addition to the errors that are already there due to the very high normal mutation rate of HIV.

For detailed scientific background, see [1].

* * *

AIDS Treatment News interviewed Dr. Stephen Becker in mid September 2007. Dr. Becker, who has been well known for years as a leading AIDS clinician and scientist, was hired last year by Koronis Pharmaceuticals, a small company in Seattle, Washington, to design and conduct the clinical trial that could lead to proof of principle of KP-1461.

Interview with Dr. Becker

AIDS Treatment News: Am I correct in believing that KP-1461 causes lots of mutations of HIV?

Dr. Becker: Yes. KP-1461 is a nucleoside analog [a false building block of the viral DNA]. It is a cytidine analog. But unlike all the conventional HIV nukes, it is not a chain terminator, it does not inhibit reverse transcription in the way that all of the conventional nukes do. It is incorporated by reverse transcriptase, and once it's incorporated, just as the transcription process would dictate, there is base-pair matching that goes on.

KP-1461 is actually a prodrug [a medicine designed to be orally usable, which changes into its active form inside the body]. The active drug, intracellularly triphosphorylated like all the other nucleosides, is KP-1212. But for ease of discussion we may call it KP-1461, even though we know that's the prodrug.

Once KP-1212 is incorporated by reverse transcriptase into the copy strand, it can

appear in one of two forms. It can appear as its native cytidine, but also can appear as a thymidine. This happens because of the flexible structure of the drug. It is able to tautomerize (the chemical term); it is incorporated as a cytidine, but then appears ambiguous to the complementary base. If it appears as a cytidine it would normally pair with a guanosine (following Watson-Crick base-pairing rules). But when it appears as a thymidine to the complementary base, it winds up pairing with adenosine, causing a base-pair mismatch. So the drug actually brings about base-pairing errors, usually guanosine->adenosine errors.

Once the wrong base is incorporated and a base-pairing error exists, it is locked into the proviral DNA. With every replication cycle, this base-pairing error is perpetuated. As the drug continues to be administered, there is a progressive accumulation of errors, throughout the viral genome. There is no preferential hot spot for incorporation; so base-pairing errors will appear in all the viral genes.

Each mutation that the virus acquires tends to reduce its fitness -- the viability, the infectivity, of the virus. So a mutational accumulation (as the theory held, and as we demonstrated in test-tube cell cultures) brings about the collapse of the viral population. If you progressively add too many mutations, you exceed an error threshold, or a threshold of viral viability, and the population collapses.

The theory for this came from Manfred Eigen -- who won the Nobel Prize for chemistry in 1967 for something called fast reactions. In the 80s and the 90s he applied his chemist's and mathematician's brain to problems in biology. At Harvard he asked biologists to tell him about the problems they wrestled with, and he came up with the theory of viruses including HIV which exist as a quasispecies -- meaning that it exists with many viral variants ('strains') in a population. Some of the strains will be very fit, infectious and pathogenic; others will be weak or have lesser degrees of fitness or infectivity. The virus has an advantage in this population form, because having certain strains with resistance mutations allows the viral population to evade selective killing pressures of HIV drugs, or of the host immune system.

So Dr. Eigen developed the concept of viral quasispecies, and suggested that if you hypermutate the virus, you could push it to the state of non-viability; you could exceed error permissiveness, you could bring about an error catastrophe in the population, and the virus would collapse. This theory has been out there for a while; Eigen published during the 1990s. And scientists from the University of Washington and MIT, (Jim Mullins, the HIV virologist, Larry Loeb, a DNA polymerase expert, an MD PhD also at University of Washington who studies mutations and cancer, and a chemist at MIT, John Essigmann), came up with the idea of fashioning a drug that could induce mutations in HIV, and helped develop KP-1461. Several series of in vitro experiments were done in cell cultures, using a very nasty strain of HIV, a homogeneous, highly fit virus. And after an average 15 serial passages, that virus was irreversibly extinguished -- repeatedly. Repeated, published experiments have demonstrated that you can collapse the viral population with KP-1461.

You and I both know that none of the HIV drugs currently marketed have been able to extinguish the virus in laboratory cultures, and certainly not in humans. They may be very potent inhibitors, but when the drug is taken away, the virus re-grows. That did not happen with KP-1461. It's distinguishing feature, from a therapeutic perspective, is that it is capable of viral eradication in vitro. We don't know if that will happen in humans; this is exactly what the current phase II clinical trial is designed to determine.

I came to Koronis Pharmaceuticals almost a year ago, to design and execute the trials that would demonstrate proof of concept of the drug. That's precisely where we are at this point. There is an ongoing phase II clinical trial; it is a very hard trial

to recruit. But we have enrolled 8 patients out of a projected enrollment of 32. They will be dosed with KP-1461 as monotherapy for four months.

The serial passage data showed extinction of the virus after 15 serial passages in the laboratory. If you use that with the David Ho - Alan Perelson calculations of HIV kinetics (and all you really can do is a back-if-an-envelope type of calculation), we think it will take a couple months to bring about an effect in humans. So the four months was chosen in part reflective of this couple months of dosing, and the fact that there is animal safety data that will permit a study of four months.

We've gone through phase I studies; a phase IA study in healthy volunteers, and a phase IB study in 50 HIV-infected individuals, similar in description to the current phase IIA subjects. They were triple-class-experienced individuals; the drug was given in the 1B study for 14 days, because that is all the animal safety data there was at that time. The bottom line for the phase I studies is that the drug appears safe and quite well tolerated.

The findings from the IA and IB and the strength of the in vitro data, including genotoxicity and mutagenesis studies done in the preclinical stage, took us to performing phase IIA studies.

ATN: What keeps KP-1461 from harming human DNA?

Dr. Becker: There are two very fundamental safety questions that people have, and this is one of them. The question is how specific a viral mutagen is this drug, to what extent is it capable of mutating host DNA, which of course would not be a good thing. The answers to that are as follows.

Genotoxicity depends on how much of the drug is incorporated by human DNA polymerase, and how much of it is excised [cut out]. In the case of human DNA in the nucleus of cells, KP-1461 is very poorly incorporated -- a log [about 10 fold] less than any of the other nucleoside analogs.

But it is incorporated to a modest degree, about as much as 3TC or tenofovir, by gamma polymerase in human mitochondrial DNA. However, it is very quickly proofread and excised. We have done those experiments, and we and the FDA are satisfied with them for dosing, at least this far in our development program.

ATN: What is the other safety issue?

Dr. Becker: The other key question that people rapidly come up with is, could you create a supervirus?

This needs to be considered. It is a concept that most of us are not familiar with. In HIV therapeutics we are trying to avoid mutations and avoid viral diversity. KP-1461 is a drug intended to create mutations and increase viral diversity. The question of whether you could create a supervirus is one that, at this time, has much less data than the viral vs. host DNA selectivity question.

We can only speak in terms of virology, HIV virology, and evolution. And these studies suggest that of 100 mutations, 49 of them are non-coding; they don't result in an altered protein in any way. These mutations do not change viral enzymes. So they are basically silent.

Fifty of the 100 mutations will reduce viral fitness. We see this all the time with HIV. A mutation in response to a drug impairs the fitness of the virus. Sometimes that fitness hit is greater (as with K65R or 184V mutations), and sometimes less; but they all impair viral fitness.

One percent of mutations are believed to increase viral fitness. So could we create a supervirus? On theoretic grounds it is possible but not likely at all. HIV has evolved to become the supervirus. Mother nature has been testing billions of mutations for decades. For example, compared to Ebola, HIV is successful because it does not kill its host in days. Evolution has selected against the most pathogenic strains that would kill the host too quickly before the virus could be transmitted throughout a human population, which is of course exactly what the virus from its perspective is trying to

do. So one could argue that mother nature has in some ways already created this supervirus. The most efficient and effective virus already exists. And 99 of 100 mutations are going to reduce the virus's fitness, not increase it.

Current Clinical Trial

ATN: Our main question is on the inclusion criteria for the trial. Patients must have had extensive antiretroviral experience, but have been off all antiretrovirals for at least 16 weeks. This seems to be difficult to find. Could you describe not just the criteria, but also the kinds of patients -- maybe they have used antiretrovirals and don't have good options, so they stopped?

Dr. Becker: I can see three general patient populations that would be suitable for this study.

One group of patients might qualify because they were treated too early in their infection, treated with less than suppressive regimens, or were not fully compliant when they were given a suppressive regimen. In the 90s we treated people with 700 T-cells and a viral load of 5,000 -- at the time, that was what we were supposed to be doing. In retrospect that was probably too early; we didn't even know whether that patient was a progressor or not. So one category would be patients who may have been treated too early, with less than fully suppressive therapy, who now have stable T-cells; they are off therapy, but they have resistant virus.

Another category of patients would be those who for whatever reasons cannot construct a regimen expected to be suppressive. That could be because they participated in an integrase trial and have integrase resistance already, or their insurance company will not cover the Trofile assay and it's not clear that they can use maraviroc -- or they are not ready to go back onto a combination of conventional antivirals -- they don't really have as many options as a genotype or phenotype might suggest, because of intolerance or allergy to some of the drugs. So that is a second general category of patient.

And the third might be patients who just do not tolerate a 3-drug or 4-drug antiretroviral regimen. If you need to use ritonavir, there are some people who cannot even take 100 mg of ritonavir without getting sick.

Those are the three general categories of patients I think would be potentially suitable for consideration. Of the eight patients we've enrolled so far, a couple fall into that treated too early, non-suppressive regimen category. And we actually have one individual who was infected with triple-class resistant virus. Even though they are not treatment experienced, I provided a waiver for that patient, because they had a terribly ugly genotype of triple-class resistant virus, though by transmission, not prior therapy.

But I wanted people to be off of therapy for sound reasons -- in this post-SMART era where almost nobody should be off therapy. I wanted to make sure that these were folks who felt, with their clinicians, that there was a solid reason to be off of antiretrovirals. I wanted them off for 16 weeks, so that they would have gone through whatever sort of reversion to wild type, and may be at a new CD4 and viral load steady state. I did not want somebody who was about to have immunological or clinical progression because their virus was suddenly very active and very pathogenic. That is why we are requiring 16 weeks off of therapy.

We require a CD4 count of at least 250 because we wanted patients who were not at proximate risk for an AIDS-defining event. Somebody with 50 T-cells would be too much at risk, and I think ought to be on some conventional therapy. One could argue that we could have set it the limit at 200 or 150, but we picked 250 for the moment.

We know that this will be a very hard study to enroll. So for 32 patients, we have 23 sites up throughout the U.S., and we will have in total probably 30 sites. So we

are just looking for one or two patients per site. We want quality not quantity; this is a different kind of study, so we approached it from the perspective of many sites with low enrollment.

ATN: How can potential volunteers find a site near them?

Dr. Becker: On **http://www.clinicaltrials.gov** search for KP-1461. This shows the current sites, and whether they are recruiting, as of the date of the last changes, which is posted on the site. Check back in case none are near you, as we are still adding more sites.

Summary

ATN: How would you summarize the importance of this study?

Dr. Becker: This drug is clearly different in concept, and clearly different in the laboratory. It must be tested; we have seen so many drugs that looked good but did not work. While the current generation of antiretrovirals is really good, eradication of the virus has been taken off of the agenda. Maybe the current drugs cannot achieve that. But we have to have eradication remain as a therapeutic imperative. It is up to creative scientists, chemist and virologists, to create drugs that can eradicate HIV. We have many things to contend with -- sanctuary sites, and latent resting reservoirs -- but who is to say that the next generation of drugs should not have eradication as its goal?

I think we will have clinical data by the second quarter of next year, to indicate whether or not we are on the right track. I want the community, doctors and patients, to be fully aware of this drug, aware of its laboratory demonstrations, and know that we are trying to test it in early stage clinically.

We don't know whether four months dosing will be enough. We came up with four months based on a back-of-the-envelope projection, and animal safety data. But it could be that 4 months is right, or 2 months is sufficient, or that your really need 10 months. We won't know that until we complete these studies.

But we will make KP-1461 available to any individual who participates in the phase II studies, should it be apparent that the drug is effective and safe, but maybe needs to be given for a longer duration. We will work with the FDA to establish a protocol that will provide drug for those who participated in our early development trials should they need further treatment. Often patients who participate in early stage studies are excluded from further access to the drug. We have committed, and put into writing, that we will establish a protocol for those who might benefit from further KP-1461 therapy.

Koronis Pharmaceuticals is a private company; there are only 17 of us. It is a very small group of people wearing many different hats. Our aspiration is not to become the next Gilead. But if this drug is active we would love to partner with larger pharma, to conduct late-stage HIV trials, which as you know is a fully international several thousand patient venture. That is nothing that a company like ours could possibly do alone.

References

1. Harris KS, Brabant W, Styrchak S, Gall A, and Daifuku R. KP-1212/1461, a nucleoside designed for the treatment of HIV by viral mutagenesis. *Antiviral Research*. July 2005; volume 67, number 1, pages 1-9.

Isentress (Raltegravir) Pricing: Community Sign-On Letter

The Fair Pricing Coalition is asking Merck to price its new and very important integrase inhibitor at a level everyone can live with. The letter is seeking organization and individual signers until the official launch of the drug, when the price will be announced.

"A new HIV drug produced by Merck is about to be approved by the Food & Drug Administration in early October. While this is great news, especially for people who have developed resistance to existing therapies, the pricing of this treatment will have a